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Endogenous ouabain and cardiomyopathy in dialysis patients

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Abstract

Background and methods—Endogenous ouabain (EO) is markedly raised in patients with chronic renal failure. As high EO induces myocardial cell hypertrophy *in vitro* and it is associated with left ventricular hypertrophy (LVH) in essential hypertensives and in patients with heart failure we investigated the relationship between plasma EO and LV mass and geometry in 156 end-stage renal disease (ESRD) patients. EO was measured by a specific radioimmunoassay and by mass spectrometry.

Results—On univariate analysis, plasma EO was directly related to LV mass ($r = 0.26$, $P = 0.001$) and LV end diastolic volume ($r = 0.25$, $P = 0.002$) and these relationships held true in multiple linear regression models including a series of potential confounders. Patients with eccentric LVH ($n = 41$, i.e. 26%) had the highest plasma levels of EO when compared to patients with other patterns of LV geometry ($P = 0.001$). Furthermore, plasma EO had diagnostic value for eccentric LVH because the area under the corresponding ROC curve (68%) was significantly greater ($P = 0.002$) than the threshold of diagnostic indifference. In this analysis, the sensitivity was 91% and the specificity was 36%. The positive predictive value was 33% but EO had a remarkably high negative predictive value (92%) for the exclusion of eccentric hypertrophy.

Conclusions—In ESRD patients, plasma EO is independently associated with LV mass, LV volume and eccentric LVH. The results of this study are compatible with the hypothesis that EO is involved in alterations of LV mass in ESRD.

Keywords

dialysis; endogenous ouabain-like factor; left ventricular end diastolic volume; left ventricular hypertrophy

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Introduction

Left ventricular hypertrophy (LVH) is a major risk factor for both overall and cardiovascular (CV) mortality in patients with end-stage renal disease (ESRD) [1, 2]. LVH in ESRD is a multifactorial disorder and several aetiological factors have been implicated in the high LV mass in this condition including hypertension, anaemia, hypoalbuminaemia, hyperparathyroidism, volume overload [3, 4] and sympathetic activity [5].

The endogenous ouabain (EO), an inhibitor of Na-K ATPase, has been found to be increased in a variety of clinical conditions including hypertension [6, 7], hyperaldosteronism [8], congestive heart failure [9] and chronic renal failure [10, 11]. In theory this compound may be implicated in alterations of LV mass and function in ESRD [12]. Indeed, it induces myocardial cell growth [13] and enhances apoptosis [14] at least `*in vitro*' models. Information on the potential role of EO in LVH in man is still sparse. In young offspring of hypertensive individuals, plasma EO levels are associated with a diastolic function pattern that precedes the development of hypertension and LVH [15]. Approximately 50% of Caucasians with uncomplicated essential hypertension show increased concentrations of EO in association with higher left ventricular mass and stroke volume [15]. Finally, in patients with idiopathic dilated cardiomyopathy, high circulating levels of EO identify those individuals predisposed to progress more rapidly to heart failure [16]. With this background in mind, we investigated the relationship between EO plasma levels with left ventricular mass and cardiac geometry in ESRD patients.

Patients and methods

Patients

One hundred and fifty-six patients on chronic dialysis treatment at the dialysis units of the CNR-IBIM Research Unit, Reggio Calabria ($n = 104$) and the Department of Nephrology San Raffaele Hospital, Milan ($n = 52$) were included in this study. Of these, 129 were on haemodialysis and 27 on Chronic Ambulatory Peritoneal Dialysis (CAPD). The cause of chronic renal disease was chronic glomerulonephritis in 38 cases, pyelonephritis/interstitial nephritis in six, polycystic kidney disease in 14, hereditary nephropathy in one, congenital renal displasia in one, vascular renal disease in 19, Wegener's granulomatosis in one, diabetes in 26, cortical necrosis in two, amyloidosis in one and undefined in the remaining 47 cases. Haemodialysis patients had a residual diuresis <300 mL day^{-1} whilst thee of the 27 CAPD patients had a diuresis >500 mL day^{-1}.

Haemodialysis patients were being treated thrice weekly with standard bicarbonate dialysis ($n = 100$), acetate-free biofiltration ($n = 1$) or high flux haemodialysis ($n = 10$) either with Cuprophan or semisynthetic membranes. The standard formula of Kt/V has been used to measure dialysis adequacy, where K stands for the dialyzer clearance, expressed in millilitres per minute, t stands for time, V is the volume of water a patient's body contains. The average Kt/V in these patients was 1.28 ± 0.32. Patients on CAPD were all on a four exchanges per day schedule with standard dialysis bags (weekly Kt/V: 1.67 ± 0.31). Seventy-four patients were on treatment with erythropoietin, 87 were taking various antihypertensive drugs (51 on monotherapy with ACE inhibitors, calcium channel blockers, alpha- and beta-blockers, furosemide and 36 on double, triple or quadruple therapy with various combinations of these drugs) and 14 were treated with digoxin. Fifty-one patients were habitual smokers. The main demographic, anthropometric, biochemical and hemodynamic data of patients are listed in Table 1.

Endogenous ouabain assay and liquid chromatography mass spectrometry

A fasting blood sampling was performed on the venous side of the non-A-V fistula arm. EO was extracted from plasma and measured by using a specific radioimmunoassay (RIA) as previously described [17]. The assay used an ouabain antiserum with low cross-reactivity for digoxin (approximately 0.42%), spironolactone (<0.01%), canrenone (<0.01%) and canrenoate (0.07%) but has no measurable interaction with any of the antihypertensive medications used by the patients. Liquid chromatography mass spectrometry (LCMS) was used to prove the presence of EO in the sample extracts from four patients whose EO was also determined by RIA. The EO content of the samples, as determined by LCMS from interpolation of an ouabain standard curve, and the results from the ouabain RIA were highly correlated ($r = 0.94$) in linear regression analysis. No molecular ions of ouabain were observed when water was used instead of plasma samples.

Echocardiography

Each patient underwent an echocardiographic study and all echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography [18] by an observer unaware of arterial pressure and biochemical results. Left ventricular mass index (LVMI) was calculated according to the Devereux formula [19]. Relative wall thickness (RWT) was calculated as: 2*Posterior wall thickness/Left ventricular end diastolic diameter (cut-off value: ≥0.45). Geometric analysis of the left ventricle was performed according to Koren *et al.* [20]. Presence or absence of LVH was defined on the basis of a LVMI ≥125 g m^{-2}. Patients with normal LVH and RWT <0.45 or >0.45 were considered to have normal LV geometry or concentric remodelling, respectively. Those with increased LVMI and RWT <0.45 or >0.45 were considered to have eccentric nondilated hypertrophy (EH) or concentric hypertrophy (CH), respectively. Cardiac index and stroke index were calculated by standard formulae.

Blood pressure measurements and antihypertensive therapy

In haemodialysis patients predialysis and postdialysis blood pressures (BPs) were calculated as the average value of all recordings [12 measurements (i.e. three per week)] taken during the month preceding the study. The mean value of predialysis and postdialysis BPs was then obtained for each patient and it was considered for global statistical assessment [21]. In CAPD patients, BP values were obtained by averaging Home Blood Pressure Measurements (10–20 measurements per month). To obtain a rough estimation of antihypertensive therapy we assigned a value of 1 to each class of antihypertensive drugs, which were being taken by dialysis patients at the time of the study considering the sum as the final score.

Effect of haemodialysis treatment on plasma EO

To determine the potential effect of dialysis treatment on plasma EO concentration, we measured plasma EO levels by RIA before and after a single haemodialysis session in a subgroup of 32 patients.

Statistical analysis

Data are expressed as mean ± SD or as median and interquartile range and comparisons between two groups were made by *t*-test or Mann–Whitney *U*-test, as appropriate. The relationship between paired variables was investigated by standard Pearson correlation coefficient. The association between EO and left ventricular geometric pattern was analysed by *P*-value for trend.

The independent relationship between plasma EO and the four-key variables (LV mass index, LV end diastolic volume, cardiac index and stroke index) was tested by multiple

linear regression analysis. A set of independent variables were identified starting with plasma EO as well as with Framingham risk factors [age, sex, smoking, diabetes, systolic pressure and number of antihypertensive drugs, serum cholesterol and body mass index (BMI)] and factors peculiar to ESRD [duration of dialysis treatment, haemoglobin, albumin and parathyroid hormone (PTH)]. Significant independent variables were identified by a stepwise approach. By this strategy we constructed models of adequate power (at least 26 patients for each variable included in the models). Data are expressed as standardized regression coefficient (β) and *P*-value.

The usefulness of plasma EO to identify EH (as previously defined) was tested by the analysis of ROC curve. The diagnostic threshold of plasma EO for eccentric LVH in dialysis patients was defined as the EO value combining better sensitivity and specificity, i.e. as the best cut-off in the ROC curve. The confidence intervals of sensitivity, specificity, positive and negative prediction values were calculated by a standard formula.

All statistical analysis was performed by spss for Windows (Version 9.0.1, 11 March 1999, Chicago, IL, USA).

Results

The demographic, clinical and echocardiographic data in the study sample are reported in Table 1. At echocardiography, the large majority of patients (72%) displayed LVH (eccentric LVH: 27%; concentric LVH: 45%). Twenty per cent had concentric LV remodelling and only a minority of patients displayed normal LVM and geometry (8%).

Plasma EO levels were three- to fourfold higher in dialysis patients (0.93 ± 0.29 nmol L^{-1}) than those previously reported in normotensive subjects (approximately 0.2 nmol L^{-1}) and in hypertensive patients (approximately 0.3 nmol L^{-1}) [22] using the same assay methodology. Plasma levels of EO were largely unaffected by treatment modality (HD = 0.94 ± 0.31 nmol L^{-1}; CAPD patients = 0.87 ± 0.19 nmol L^{-1}, P = NS) and Kt/V (HD: r = 0.008, P = NS; CAPD: r = −0.19, P = NS) as well as by haemodialysis procedure (before HD: 1.07 ± 0.40 nmol L^{-1} versus after HD: 1.13 ± 0.45 nmol L^{-1}, P = NS). Plasma EO was related inversely with BMI (r = −0.30, P < 0.001) and directly with male sex (r = 0.23, P < 0.01) but it was largely unrelated to systolic (r = 0.005) and diastolic pressures (r = 0.09). Plasma EO was higher in patients on digoxin treatment (1.22 ± 0.26 nmol L^{-1}) than in those without this drug (0.90 ± 0.28 nmol L^{-1}). However, an analysis excluding patients on digoxin treatment (n = 14) did not materially change the average value of plasma EO in the dialysis population (0.90 ± 0.28 nmol L^{-1} vs. 0.93 ± 0.23 nmol L^{-1}).

Plasma EO and left ventricular mass and geometry

On univariate analysis, plasma EO was significantly related to LVMI (r = 0.26, P = 0.001; Fig. 1a), LV end diastolic volume (r = 0.25, P = 0.002; Fig. 1b), cardiac index (r = 0.17, P = 0.04) and stroke volume index (r = 0.17, P = 0.03). In multiple linear regression models, including a series of potential confounders (Table 2), plasma EO maintained an independent association with LVMI (β = 0.18, P = 0.02), LV end diastolic volume (β = 0.15, P = 0.05) and cardiac index (β = 0.20, P = 0.007), whereas the link between plasma OE and stroke index was no longer statistically significant after multiple data adjustment (β = 0.11, P = 0.16). Data analysis according to left ventricular geometric pattern revealed that patients with eccentric LVH had the highest plasma levels of EO (Fig. 2).

Diagnostic value of plasma EO concentration for eccentric LVH

To test the diagnostic value of plasma EO for eccentric LVH we used the ROC curve analysis. Plasma EO was of diagnostic usefulness for the identification of EH because the

area under the corresponding ROC curve (68%) was significantly ($P = 0.002$) greater than the threshold of diagnostic indifference (50%). The sensitivity was 91% (95% CI: 82–100%) and the specificity was 36% (95% CI: 27–45%). The positive predictive value was rather low (33%, 95% CI: 24–42%) but EO had a remarkably high negative predictive value (92%, 95% CI: 84–100%) for the exclusion of EH.

Discussion

The main finding of the present study is that plasma EO is independently associated with left ventricular mass and geometry in ESRD patients and that this association is independent of arterial pressure and other well-established determinants of left ventricular mass.

In ESRD, LVH and high CV risk in general represent multifactorial problems. Blood pressure, anaemia [23], hypoalbuminaemia, dyslipidaemia, hyperparathyroidism [3, 24] and high sympathetic activity [5] all contribute to increased CV risk and LVH in these patients. In the present study, we once again confirm that systolic pressure, haemoglobin and cholesterol impact upon LVH in ESRD. Our novel finding that EO is associated with LVH and that it is a marker of EH is fully in keeping with the notion that chronic volume overload is a potent stimulus for the regulation of steady-state levels of EO [25]. A reduced capacity of the ventricular wall to develop hyperthrophy [13] and cardiomyocyte apoptosis triggered by ouabain [14] remain as hypothetical possibilities for the explanation of the eccentric LVH–EO link in ESRD. Our recent findings in patients with idiopathic dilated cardiomyopathy are consistent with this interpretation [16].

Studies in normal individuals [26] and in patients with essential hypertension [22] have shown that sustained variations in dietary salt intake stimulate plasma EO. The association between EO and left ventricular end diastolic volume found in the present study supports the view that chronic volume expansion is a stimulus to EO secretion in these patients. Although associations do not necessarily imply causation, a number of observations lend support to the hypothesis that the increased EO levels are implicated in the ventricular alterations of ESRD. First, EO causes cardiomyocyte hypertrophy *in vitro* [13] and chronic infusion of ouabain in rats triggers a cellular signal cascade leading to cell hypertrophy [27], an effect which can be inhibited by a selective ouabain antagonist [27]. Secondly, in humans from the very early stages of hypertension to established hypertension, a consistent association was found between plasma EO and structural and functional ventricular abnormalities [9, 15, 27, 28].

Our data are compatible with the hypothesis that chronic volume overload is a stimulus for EO release and that this factor is implicated in myocardiopathy in ESRD [12]. However, we also found that plasma EO changed little after dialysis. This observation suggests that long-term rather than short-term changes in circulating blood volume modulate EO in ESRD patients. Plasma EO bore no relationship with plasma urea or with the administered dialysis dose (Kt/V) implying that extracorporeal clearance has no major impact on EO plasma levels in these patients. Digoxin intoxication in ESRD patients' hemoperfusion with charcoal is needed to remove this drug [29].

The ESRD patients on chronic digoxin therapy had higher plasma level of EO than those not taking this drug. The EO assay used an ouabain antiserum had low cross-reactivity for digoxin (approximately 0.4%) [15]. Hence, the increased EO observed in the digoxin-treated patients is unlikely to reflect a cross-reaction with digoxin. We believe that higher EO levels in patients on digoxin reflect a more severe degree of the underlying cardiomyopathy rather than technical problems of the assay.

In conclusion, circulating levels of EO are markedly increased in dialysis patients. Plasma EO is associated with left ventricular mass and this relationship is independent of arterial pressure and other established determinants of left ventricular mass in this population. The observation that plasma EO concentrations are higher in ESRD patients with eccentric LVH than in those with concentric LVH suggests that EO might modulate the cardiac effects of volume overload and indicates that EO is a biochemical marker of eccentric LVH in ESRD.

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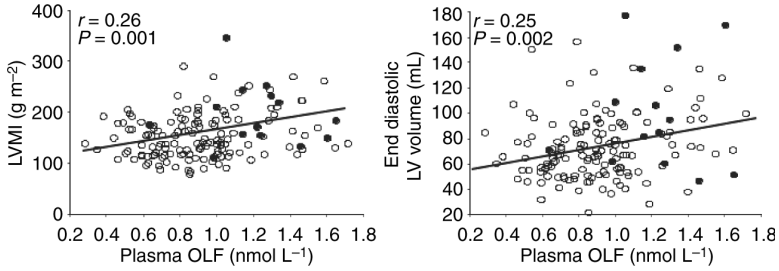

Fig. 1.

Relationships between plasma endogenous ouabain with left ventricular mass index (left panel), and left ventricular end diastolic volume (right panel). Dark circle identifies patients on treatment with digozin.

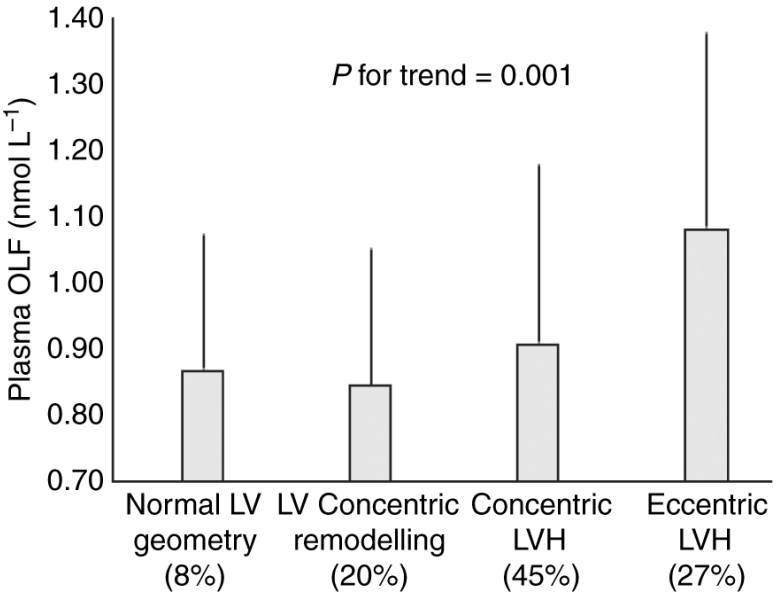

Fig. 2.
Relationship between plasma endogenous ouabain and left ventricular geometric patterns amongst dialysis patients. Data are mean ± SD and *P*-value for trend.

Table 1

Clinical characteristics of 156 ESRD patients

Age (years)	59 ± 14
Duration of dialysis (months)	45 (18–101)
BMI (kg m^{-2})	24.6 ± 4.6
Haemoglobin (g dL^{-1})	10.1 ± 2.0
Serum potassium (mEq L^{-1})	5.1 ± 0.9
Serum albumin (g dL^{-1})	3.9 ± 0.6
Serum cholesterol (mg dL^{-1})	206 ± 58
Serum triglycerides (mg dL^{-1})	179 ± 98
Systolic pressure (mmHg)	146 ± 22
Diastolic pressure (mmHg)	78 ± 13
Heart rate (bpm)	81 ± 10
Left ventricular end diastolic diameter (cm)	5.1 ± 0.8
Inter-ventricular septum thickness (cm)	1.3 ± 0.2
Posterior wall thickness (cm)	1.2 ± 0.2
Left ventricular mass (g)	264.5 ± 79.6
Left ventricular mass index (g m^{-2})	157.1 ± 46.7
Left ventricular end diastolic volume (mL)	74.9 ± 27.6
Cardiac index (L*min – 1 m^{-2})	3.32 ± 1.14
Stroke volume index (mL m^{-2})	41.3 ± 13.7

Data are expressed as mean ± SD or as median and interquartile range, as appropriate.

ESRD, end-stage renal disease; BMI, body mass index.

Table 2

Multiple linear regression analysis

Independent variables	β	*P*-value
(a) Dependent variable: left ventricular mass index (multiple $r = 0.54$, $P < 0.001$)[a]		
Systolic pressure (mmHg)	0.34	<0.001
Treatment with digoxin (0 = no; 1 = yes)	0.21	0.006
Plasma EO (nmol L^{-1})	0.17	0.02
Cholesterol (mg dL^{-1})	−0.17	0.02
Smoking	0.16	0.03
Haemoglobin (g dL^{-1})	−0.14	0.05
(b) Dependent variable: left ventricular end diastolic volume (multiple $r = 0.41$, $P < 0.001$)[b]		
Cholesterol (mg dL^{-1})	−0.21	0.006
On treatment with digoxin (0 = no; 1 = yes)	0.19	0.01
Duration of dialysis treatment (months)	−0.18	0.02
Plasma EO (nmol L^{-1})	0.15	0.05
(c) Dependent variable: cardiac index (multiple $r = 0.43$, $P < 0.001$)[c]		
Systolic pressure (mmHg)	0.27	<0.001
Haemoglobin (g dL^{-1})	−0.22	0.004
Plasma EO (nmol L^{-1})	0.19	0.01
Age (years)	−0.17	0.03

Data are expressed as standardized regression coefficient (β) and *P*-value.

EO, endogenous ouabain; BMI, body mass index.

[a]Out of the model: diabetes, albumin, antihypertensive drugs score, treatment modality, duration of dialysis treatment, sex, age, PTH and BMI.

[b]Out of the model: age, antihypertensive drugs score, sex, BMI. systolic pressure, PTH, albumin, diabetes, haemoglobin, treatment modality and smoking.

[c]Out of the model: cholesterol, duration of dialysis, sex, albumin, BMI, antihypertensive drugs score, treatment modality, smoking, PTH and diabetes.